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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/104,340	06/25/98	BOYD A	FISHR11.001A

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EXAMINER
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ART UNIT	PAPER NUMBER
1646	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/104,340	Boyd et al
Examiner	**Art Unit**
Nirmal. S. Basi	1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 24, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12, 20-24, 34-36, 39, 40, 43, and 44* is/are pending in the application.

4a) Of the above, claim(s) *9-12, 21-24, and 43* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 20, 34-36, 39, 40, and 44* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Amendments filed 3/28/00 (paper number 10), 8/25/00 (paper number 14), 9/19/00 (paper number 15), 4/23/01 (paper number 17), and 5/24/01 (paper number 18) have been entered.

2. As indicated in paper number 8 (10/25/00) the claims added as 35-43 in Paper No. 7 (7/26/99) were renumbered as 34-42. The Application contained claims 1-33, prior to the entry of the Amendment in Paper No. 7. Applicant should have continued numbering the claims as 33-42. Claim 44, added in paper number 10, has been renumbered to claim 43, and claim 45, added in paper number 15, has been changed to claim 44. In further correspondence with the Office Applicant should refer to claims, as renumbered under Rule 1.26. Amended claims 9-12, and newly added claims 43-44 (renumbered, as indicated above will not be examined because it is directed to a non-elected invention, i.e. the invention of Group II.

Specification

3. FIG. 10E remains objected to because it must be must described separately in the Brief Description of the Drawings. The description of FIG. 10E is missing in the specification. Appropriate correction is required.

In the "REMARKS" section, Applicant indicated page 35 was missing, as indicated by Examiner, in paper number 8 (10/25/99), page 25 is missing.

Claim Rejection, 35 U.S.C. 112

4. Claims 1-8, 20, 34-36, 39-40 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant argues that "an Eph family RTK" has been removed from amended claim 1 and replaced with "an Eph receptor tyrosine kinase gene". Applicant has amended claims 2 and 6 to include "an Eph family tyrosine kinase". Claims 1, 2, and 6 are indefinite because it is not clear what comprises a "an Eph receptor tyrosine kinase gene" and "an Eph family tyrosine kinase" so as to allow the metes and bounds of the claim to be determined. Applicants arguments (paper numbers 10,14,15,17 and 18), and the declaration of Andrew Wallace Boyd (paper number 11, 3/28/00) have been fully considered but not found persuasive. The declaration of Andrew Boyd discloses the term Eph family tyrosine kinase "has a precise and definite meaning in the art", and goes on to disclose structural and functional features of the genus of "all Eph family members". Andrew Boyd discloses one of the common features of all Eph family members is "a typical tyrosine kinase catalytic domain". Pasquale (Ref D6, Appendex A, Current Opinion in Cell Biology, 1997, 9:608:615), also describes common features of the "Eph family", some of which are similar to those of Andrew Boyd. In contradiction, Pasquale states, "many receptor variant forms also exist", referring to Eph family members, "that do not conform to the prototypical domain structure, as they contain deletions, truncations, substitutions, or insertions", and further states, "One Eph receptor, Mep, lacks kinase activity". Therefore the claims, specification, the declaration of Andrew Boyd nor prior art provide a clear unambiguous disclose what constitutes the "an Eph family tyrosine kinase", which in turn

is encoded by "an Eph receptor tyrosine kinase gene", so as to allow the metes and bounds of the claim to be determined.

Claims 1 is indefinite because it is not clear what amino acids comprises a "exon I", "exon II" and "exon III" of an Eph receptor tyrosine kinase so as to allow the metes and bounds of the claim to be determined. To determine what amino acid sequence is encoded by an "exon" then it must be apparent what nucleotide sequence comprises the "intron". The metes and bounds of the "exon"cannot be determined without knowledge of the "introns". Although over fourteen Eph family members were known at the time of filing of instant Application, most did not have their genomic organization elucidated (ie Eph tyrosine kinase gene). The first Eph family member gene was isolated by Connor et al (Ref D19, Appendex A, Oncogene, 1995, 11, 2429-2438), and even the then, Conner states, "Since genomic sequences upstream of initiation ATG were not identified, exon numbering was on the assumption that the first exon contains the 5' untranslated sequence as well as the sequences encoding the signal peptide", page 2430, column 2, first paragraph.

Claims 1 and 5 are indefinite because it is not clear how many amino acid residues are encompassed by the term "consisting essentially of", when referring to the amino acid sequence, so as to allow the metes and bounds of the claim to be determined. It is not clear when a polypeptide consists essentially of the exons disclosed in the claims as compared to when said polypeptide does not essentially consist of said exons.

Claim 2 is indefinite because it recites "excludes the entire extracellular domain of an Eph Family receptor tyrosine kinase". The entire extracellular domain of an Eph Family receptor tyrosine

kinase is disclosed by Applicant to contain exons I-III. Claim 1 is directed to the polypeptide consisting essentially of exons I-III, whereas dependent claim 2 excludes said polypeptide. Therefore the claim is ambiguous in nature. Similarly claim 6 is indefinite for excluding the entire extracellular domain of an Eph Family receptor tyrosine kinase.

Claims 3, 4, 7 8, 20, 34-36, 40-41 and 44 are rejected for depending upon an indefinite base (or intermediate) claim and it fails to resolve the issues raised above.

35 U.S.C. § 112, first paragraph

5. Claims 1-8, 20, 34-36, 39-40 and 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide, wherein the polypeptide comprises an amino acid sequence disclosed in SEQ ID NO:4 or encoded by SEQ ID NO:5 (i.e. encoded by exons I-III of HEK), wherein said polypeptide binds LERK 3, LERK4 LERK5 and LERK7, does not reasonably provide enablement for other polypeptides. The, specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant argues "the specification teaches a principle that can readily be put into practical effect without undue experimentation on the part of the skilled person" and , "a clear teaching of the present invention is that exons I, II and III of Eph family RTK genes are structurally-defines elements which correlate with structural domains of the encoded polypeptide". Applicants arguments have been fully considered but not found persuasive. Contrary to Applicants arguments the intron/exon structure of

most Eph family RTK genes encompassed by the claims was not known at the time of filing of instant Application. Applicant only discloses the exons of HEK, and provides no structure for the introns. Owshalimer et al (Ref D21, Appendex A, Molecular and Cellular Probes (1999) 13, 169-173) disclose the complete intron/exon structure of the EPHA1, eleven years after isolation of the EPHA1. Owshalimer discloses the complex nature of identifying and assigning exon/intron regions to the isolated gene, and further the difficulties in relating the structures from one gene to another. For example, Owshalimer discloses, primers do not amplify certain regions of the gene, coding regions contained variations from the published EPHA1 sequence which could result in reading frame shift. Owshalimer, further states "Eighteen coding exons were identified, two more than the related EPHB2. There may also be non-coding exons upstream of exon 1, as this region was not sequenced. Alignment of EPHA1 and EPHB2 cDNA's indicate that EPHA1 exons 3-4 and 12-13 correspond to a single exon each in EPHB2" (page 172). Further it is not clear what protein is claimed, in claims 2 and 6, which contains the limitation of excluding the entire extracellular domain of an Eph Family receptor tyrosine kinase. Exons I-III are in the extracellular domain.

While the person of ordinary skill in the art would, in light of the specification be able to isolate a polypeptide of SEQ ID NO:4, encoded by SEQ ID NO:5 (i.e. encoded by exons I-III of HEK), wherein the polypeptide binds LERK 3, LERK4 LERK5 and LERK7, the scope of the claims, which encompass other polypeptides containing other exons with LERK 3, LERK4 LERK5 and LERK7 binding activity are not enabled by the disclosure. The disclosure does not teach how to use a commensurate number of the polypeptides which do not share the LERK 3, LERK4 LERK5 and

LERK7 binding activity functions. The disclosure teaches the binding of LERK7 to HEK encoded by exons I-III and further discloses that LERK7 does not bind to polypeptide encoded by exons I-II (FIG. 2F). Also disclosed is, "no expression was observed for any of the protein constructs containing the exon III encoded domain, but missing the first 31 amino acids of the mature HEK protein (encoded by exons I and II; amino acids 21-25 of the sequence shown in FIG. 1)", see page 38, line 17 -23. Therefore, the specification discloses the interaction of LERK7 with the domain of the HEX protein encoded by exons I-III but also suggests that said domain is critical for binding of LERK7. The disclosure fails to teach how to use to use a commensurate number of the polypeptides which do not share the LERK 3, LERK4 LERK5 and LERK7 binding activity functions.

Therefore, due to the large quantity of experimentation necessary to identify the polypeptides containing the exons claimed, the lack of direction/guidance presented in the specification regarding the identification, purification, isolation and characterization of said polypeptides, the unpredictability of the effects of mutation on the structure and function of proteins (since mutations of SEQ ID NO:4 are also encompassed by the claim), no clear disclosure that exon II alone or ExonII/Exon III will bind LERK, the unpredictability in the art for correlating different Exons from different Eph receptor tyrosine kinase genes to generate functional protein, and the breadth of the claim which fail to recite specific functional limitations, undue experimentation would be required of the skilled artisan to make or use the claimed invention in its full scope.

6. **Claim Rejections, 35 U.S.C. 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-8, 20, 34-36, 39-40 and 44 rejected under 35 U.S.C. 102(e) as being anticipated by Boyd et al (Ref B, U. S. Patent No. 5,674,691, see previous Office Action, 10/25/99).

Applicant argues since the claims now recite "polypeptide consisting essentially of an amino acid sequence encoded by exon III or by exon III, II, I" the claims necessarily excludes the extracellular domain of HEK. Applicants arguments have been fully considered but not found persuasive. The polypeptide of Boyd et al is identical to the that described in instant application and therefore expected to have the same exon structure. Further the term "polypeptide consisting essentially of" encompasses the protein of Boyd.

Boyd et al teach the polypeptide of SEQ ID NOs: 1-4 encoded the polynucleotide of SEQ ID NOs: 5-8 (see SEQ ID NOs :9 and 10). The sequences disclosed by Boyd et al are for HEK.. The receptor-type tyrosine kinase (HEK) is identified as a member of the eph/elk family of tyrosine kinases (column 1, last paragraph). Further disclosed is "ligands for HEK are capable of being screened for in a number of ways"(column 6, last paragraph). Also disclosed is that the fusion protein can be used to assay ligand activity (column 6, first paragraph and last paragraph). Column 11, second paragraph discloses the structural features of HEX which include, signal peptide,

transmembrane domain, extracellular domain which is rich in cysteine residues. The disclosure of Boyd et al meets all the limitations of claims 1-8, 20, 34-36, 39-40 and 44 since the disclosed extracellular domain comprises or has the domains encoded by exons I-III of instant invention.

7. Claims 1-6, 20, 34-36, 39-40 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claims are drawn to isolated polypeptide which is capable of binding a LERK, said polypeptide consisting essentially of an amino acid sequence encoded by exons selected from the group consisting of :

a) Exon II of an EPH receptor tyrosine kinase gene, Exon II and Exon III of an EPH receptor tyrosine kinase gene, and exon I, Exon II and Exon III of an EPH receptor tyrosine kinase gene

b) wherein the LERK is selected from LERK3-LERK7.

The specification discloses a polypeptide of SEQ ID NO:4, encoded by SEQ ID NO:5 (i.e. encoded by exons I-III of HEK), wherein the polypeptide binds LERK 3, LERK4 LERK5 and LERK7. The instant disclosure of one distinct polypeptide does not adequately describe the scope

of the claimed genus, which encompasses a substantial variety of subgenera including full-length, truncated, fusion polypeptides and variants. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by an amino acid sequence, falling within the scope of the genus or of a recitation of structural and functional features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The mere disclosure of Exon I-III is insufficient to encompass all said exons in other related proteins. To determine what amino acid sequence is encoded by an "exon" then it must be apparent what nucleotide sequence comprises the "intron". Although over fourteen Eph family members were known at the time of filing of instant Application, most did not have their genomic organization elucidated (ie Eph tyrosine kinase gene). The first Eph family member gene was isolated by Connor et al (Oncogene, 1995, 11, 2429-2438), and even the then, Conner states, "Since genomic sequences upstream of initiation ATG were not identified, exon numbering was on the assumption that the first exon contains the 5' untranslated sequence as well as the sequences encoding the signal peptide", page 2430, column 2, first paragraph. The intron/exon structure of most Eph family RTK genes encompassed by the claims was not known at the time of filing of instant Application. Applicant only discloses the exons of HEK, and provides no structure for the introns. Owshalimer

et al (Molecular and Cellular Probes (1999) 13, 169-173) disclose the complete intron/exon structure of the EPHA1, eleven years after isolation of the EPHA1. Owshalimer discloses the complex nature of identifying and assigning exon/intron regions to the isolated gene, and further the difficulties in relating the structures from one gene to another. For example, Owshalimer discloses, primers do not amplify certain regions of the gene, coding regions contained variations from the published EPHA1 sequence which could result in reading frame shift. Owshalimer, further states "Eighteen coding exons were identified, two more than the related EPHB2. There may also be non-coding exons upstream of exon 1, as this region was not sequenced. Alignment of EPHA1 and EPHB2 cDNA's indicate that EPHA1 exons 3-4 and 12-13 correspond to a single exon each in EPHB2" (page 172). Therefore Exons from one EPH tyrosine kinase gene cannot be readily correlated those of another EPH receptor tyrosine kinase gene with the expectation of having the same effect. Application nor prior art provide compensatory structural or correlative teachings of EPH receptor tyrosine kinase gene intron/exon structure to enable one of skill to isolate and identify the polypeptides encompassed to predictably identify the encompassed molecules as being identical to those instantly claimed.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus,

the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In instant case the complete intron/exon structures of the genes encompassed by the claims is required. Accordingly, the specification does not provide a written description of the invention of claims 1-6, 20, 34-36, 39-40 and 44.

8. Claims 2 and 6 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 2 and 6 encompasses an "isolated polypeptide excluding the entire extracellular domain of an Eph Family receptor tyrosine kinase". There is no support for the statement "isolated polypeptide excluding the entire extracellular domain of an Eph Family receptor tyrosine kinase" in the specification.

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal Basi whose telephone number is (703) 308-9435. The examiner can normally be reached on Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for this Group is (703) 308-0294.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nirmal S. Basi
Art Unit 1646
August 13, 2001

Yvonne Eyler

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